REMARKS/ARGUMENTS

Claims 1-6, 8, 11-20, 32-39, 41, 80, 82-95, and 105 remain in this application. Claims 7, 9, 10, 21-31, 40, 42-79, 81 and 96-104 are withdrawn as being drawn to a non-elected species. Applicant reserves the right to pursue the withdrawn claims in continuation or divisional applications. No claims have been amended. No claims have been allowed.

Claim Rejections Under U.S.C. §102

Claims 1, 2, 12, 13 and 19 are rejected under U.S.C. §102(a) as being anticipated by Affhotler et al. (WO 98/36080). Examiner asserts that Affhotler et al. discloses a method of producing a modified gene fusion construct, comprising cojoining two heterologous nucleic acid sequences, wherein each sequence encodes one or more enzymatic domains, and wherein at least one of the two or more heterologous nucleic acid sequences is modified, that the two heterologous nucleic acid sequences encode thioredoxin and dehalogenase, that the nucleic acid sequence encoding the dehalogenase is modified, that the two sequences are connencted by one or more nucleotide linker sequences which comprise a restriction enzyme recognition site, and therefore it is estimated to be between 3 and 200 nucleotides in length, and that the modified gene fusion construct comprises one or more transcription regulatory sequences.

Claims 1, 2, 4, 11-14, 16-20 are rejected under 35 U.S.C. §102(b) as being anticipated by Gilbert et al. (WO99/31224-A). Examiner asserts that Gilbert et al. disclose a method of producing a modified gene fusion construct, comprising cojoining two or more heterologous nucleic acid sequences wherein each sequence encodes one or more enzymatic domains, and wherein at least one other two or more heterologous nucleic acid sequences is modified, that the two nucleic acid sequences encode such enzymes as glycosyltransferase or

sialtransferase and an accessory enzyme such as glucokinase or sialylsynthetase, that the nucleic acids are modified since a region encoding a His tag is added, restriction sites are added, a peptide linker, and a c-Myc epitope tag is added. Also the Examiner asserts, that the modified heterologous genes may be considered to be linked directly to each other, since the modified heterologous gene can be considered to encompass the original gene sequence with the peptide linker. In addition, the Examiner states that the reference discloses a peptide linker that comprises 4, 8, or 9 amino acids, which thus falls within the limits of 3-300 or 12-90 nucleotides, that the reference teaches that the linker may be a poly-glycine peptide, that the reference discloses that the linker may comprise a cleavage site, that the reference discloses the method in which the fusion construct further comprises one or more transcription regulatory sequences, and that the transcription regulatory sequence may be from a plant.

Claims 1-5 are rejected under 35 U.S.C. §102(b) as being anticipated by Nixon et al. (Tibtech 1998, 16:258-264). The Examiner asserts that Nixon et al disclose a method of producing a modified gene fusion construct comprising cojoining two or more heterologous nucleic acid sequences, each of which encodes one or more enzymatic domains, and at least one of which is modified, and that the reference discloses the method of producing a hybrid enzyme by the stochastic approach of DNA shuffling.

Claims 1, 4, 11, 19, 20, 32-38, 80, 82, 83, 94, and 95 are rejected under 35 U.S.C. §102(e) as being anticipated by Coruzzi et al. (US Patent 6,864, 405). Examiner states that the reference discloses a method of producing a modified gene fusion construct comprising cojoining two or more heterologous nucleic acid sequences each encoding an enzymatic domain, wherein at least one is from a plant, and the regulatory sequence is from a plant. Examiner also asserts that the enzymatic domains may be from the same or different organisms and may include modifications in such residues as those involved in substrate

binding and/or catalysis, and that the reference discloses that one of the enzymatic domains may be from a plant, that a plant promoter may be used, and that the reference discloses the direct linkage of the domains.

Claims 1-4, 11-14, 16, and 19-20 are rejected under 35 U.S.C. §102(a) as being anticipated by Peoples (WO 00/06747). Examiner asserts that Peoples et al. discloses a method of making a modified gene fusion construct comprising cojoining two or more heterologous nucleic acid sequences, wherein each encodes on or more enzymatic domains, and that at least one is modified. Examiner further states that the reference discloses that linkers may or may not be added and discloses that linkers of any appropriate length, such as 6 or 15 nucleotides may be used. Further the Examiner asserts that the reference discloses that the nucleic acid sequences may be those that participate in the same metabolic pathway, that the reference discloses that the two enzymes may be modified by gene shuffling, and that the reference discloses the method in which the gene fusion construct comprises a transcriptional regulator sequence, which may be from a plant.

Claims 1, 2, 12-15, 19, 20, 32-35, 38, 80, 83, 87-90, 94 and 95 are rejected under 35 U.S.C. §102(b) as being anticipated by Rose et al. (US Patent 5,861, 277). Examiner asserts that Rose et al. disclose a method of producing a gene fusion construct comprising cojoining two or more nucleic acid sequences encoding at least two enzymatic domains, wherein one sequence is from a plant and the other is from a prokaryote. The Examiner states that the nucleic acid sequences are modified since they contain deletions, that they are connected by a linker which comprises one or more intron sequences, that the construct comprises a plant transcription regulatory sequence, i.e. the PAT1 promoter, and that the first intron contains 110 nucleotides.

Applicant respectfully traverses all such 102 rejections.

As written by the Federal Circuit:

To constitute an anticipation a reference must disclose within its four corners each and every element of the claimed invention. Structural Rubber Products Co. v. Park Rubber Co., 749 F.2d 707, 223 U.S.P.Q. 1264 (Fed. Cir. 1984); Titanium Metals Corp. v. Banner, 778 F.2d 775, 227 U.S.P.Q. 773 (Fed. Cir. 1985); Hybritech Inc. v. Monoclonal Antibodies Inc., 802 F.2d 1367, 231 U.S.P.Q. 81 (Fed. Cir. 1986).

As stated:

"[a]nticipation requires the disclosure in a single prior art reference of each element of the claim under consideration"

In W.L. Gore & Assoc. V. Garlock, Inc., 721 F.2d 1540. 220 USPQ 303, 313 (Fed. Cir. 1983)

Additionally:

the prior art reference must disclose each element of the claimed invention "arranged as in the claim."

In Lindermann Mashinenfabrik GmbH v. American Hoist & Derrick Co., 730 F. 2d. 1452, 221 USPQ 481, 485 (Fed. Cir. 1984)

Applicant submits that none of the disclosures by Affhotler et al. (WO 98/36080), Gilbert et al. (WO99/31224-A), Nixon et al. (Tibtech 1998, 16:258-264), Coruzzi et al. (US Patent 6,864, 405), Peoples et al.(WO 00/06747) , or Rose et al. (US Patent 5,861, 277), teach all claim limitations, and none anticipates the currently claimed subject matter of the invention. Applicant respectfully requests that the rejection of the claims under 35 U.S.C. §102, be withdrawn.

Claim rejections under U.S.C. §103, Obviousness

The Examiner indicates that, because the application names joint inventors, Applicant is obligated under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 USC §103(c) and potential 35 USC §102(e), (f), or (g) prior art under 35 USC §103(a). Applicants advise the Examiner that the subject matter of the claims was commonly owned at the time any inventions covered therein were made.

Claim 6 is rejected under 35 U.S.C §103(a), as being unpatentable over Peoples et al. (WO 00/06747) in view of Minshull et al. (WO 97/35966). Examiner states that it would have been obvious to one of ordinary skill in the art, to have utilized such well known techniques of gene shuffling as recursive sequence recombination, as taught by Minshull et al., in the method of producing a modified gene fusion construct as taught by Peoples et al., since both references disclose the desirability of altering a gene sequence of interest in order to produce an improved, or altered enzyme product, by the general method of gene shuffling. Examiner states that one would have been motivated to do so by the known advantage, disclosed by Minshull et al., of the ability to recombine a large number of mutations in a minimum number of selection cycles.

Claim 8 is rejected under 35 U.S.C §103(a), as being unpatentable over Bulow er al. (Trends in Biotech. 9:226-231, 1991) in view of Goller er al. (FEMS Micro. Lett. 161 293-300, 1998), Louis et al. (Microbiology, 143:1141-1149, 1997), and Nakayama et al (Plant Physiol. 122, 1239-1247, 2000). Examiner states that it would have been obvious to one of ordinary skill in the art to combine the teachings of Bulow et al., and Goller et al., Louis et el., or Nakayama et al., for a method of producing a modified gene fusion construct, in which the genes encoding the enzymes involved in the ectoine synthesis

pathway, are conjoined to produce a modified gene fusion construct, since all of the references are concerned with the synthesis of biologically useful products using the cloned genes encoding enzymes involved in the biosynthetic pathway of said products. Examiner assets that one would have been motivated to have used the method disclosed by Bulow et al., for the production of a gene fusion construct comprising the biosynthetic enzyme encoding genes disclosed by Goller et al., Louis et al, or Nakayama et al., since they each disclose the usefulness of ectoine in osmoadaptation , and further that the expression of the enzymes encoded by the disclosed genes is desirable in heterologous cells such as plants, and since Bulow et al. disclose the desirability of expressing any biosynthetic enzyme encoding genes involved in a single pathway, together in a gene fusion construct, in order to obtain the benefit of facilitated purification, favorable enzyme kinetics, and proximity effects whereby an intermediate product can be transferred efficiently to the desired second enzyme, instead of a competing enzyme, and that based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Claim 15 is rejected under 35 U.S.C §103(a), as being unpatentable over Gilbert et al. (WO 99/31224) in view of Rose et al. (US Patent 5,861, 277). Examiner states that it would have been obvious to one of ordinary skill in the art to have modified the method of producing a gene fusion construct comprising two heterologous nucleic acids connected by a linker, by using a linker comprising an intron, as disclosed by Rose et al., since both the references disclose methods of producing constructs comprising nucleic acids which link two heterologous nucleic acids of interest. Examiner asserts that one would have been motivated to do so by the teaching of Rose et al., that the use of an intron in linker sequence results in the higher levels of expression, and that based upon

the teachings of the cited reference, the high skill on one of ordinary skill in the art, and absent evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Claims 84 and 85 are rejected under 35 U.S.C. §102(e) as being anticipated by Coruzzi et al. (US Patent 6,864, 405) or Rose et al. (US Patent 5,861, 277) in view of Minshull et al. (WO 97/35966). Examiner states that it would have been obvious to one of ordinary skill in the art, to have utilized such well known techniques of gene shuffling as recursive sequence recombination, as taught by Minshull et al., in the method of producing a modified gene fusion construct as taught by Coruzzi et al., or Rose et al, since both references disclose the desirability of altering a gene sequence of interest in order to produce an improved, or altered enzyme product. One would have been motivated to do so by the known advantage, disclosed by Minshull et al., of the ability to recombine a large number of mutations in a minimum number of selection cycles when using the method of recursive sequence recombination generally to alter the structure and function of any protein or enzyme of interest in order to obtain the benefit of improved function, and that based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent evidence to the contrary, there would have been a reasonable expectation of success.

Claims 92 and 93 are rejected under 35 U.S.C. §103 (a) as being unpatentable over Coruzzi et al. (US 6,864, 405) or Rose et al. (US Patent 5,861,277) in view of Gilbert et al. (WO 99/31224-A). Examiner states that in would have been obvious to one of ordinary skill in the art to have combined the teachings of Coruzzi et al., Rose and Gilbert et al., to produce a method of making, since all of the references teach methods of making a modified gene fusion construct in which two heterologous nucleic acids encode at least two enzymatic domains. One would have been motivated to have included such well

known peptide linker regions as those including cleavable sites, or those comprising poly-glycine, in order to obtain the benefits of obtaining separate enzymes when desired, and to obtain the known structural properties resulting from peptides rich in glycine, which include flexibility as taught by Gilbert. Examiner asserts that based upon the teachings of the cited reference, the high skill of one of ordinary skill in the art, and absent evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Applicant traverses.

The Federal Circuit has held:

"Obviousness cannot be established by combining the teaching of the prior art to produce the claimed invention, absent some teaching or suggestion supporting the combination. Under section 103, teachings of references can be combined only if there is some suggestion or incentive to do so."

ACS Hosp. Sys., Inc. v. Montefiore Hosp., 732 F.2d 1572, 221 USPQ 929 (Fed. Cir. 1984).

Also

"The mere fact that the prior art may be modified in the manner suggested by the Examiner does not make the modification obvious unless the prior art suggested the desirability of the modification."

In re Fitch., 972 F.2d 1260, 23 USPQ 2d 1780 (Fed. Cir. 1992)

In addition

"It is impermissible to use the claimed invention as an instruction manual or "template" to piece together the teachings of the prior art so that the claimed invention is rendered obvious. This court has previously stated

that "[o]ne cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention" *In re Fitch*, 972, F.2d 1260, 23 USPQ 2d 1780, 1784 (Fed. Cir. 1992) (quoting *In re Fine*, 837 F.2d 1071, 1075 5 USPQ 2d 1596, 1600 (Fed. Cir. 1988)

It is respectfully submitted that there is no suggestion to combine the references. Even if the references are combined they do not teach the method of sequence shuffling to obtain modified gene fusion constructs having enhanced activity taught in this specification.

The Federal Circuit has stated that "obvious to try" does not constitute obviousness. In re Deuel, 51 F.3d 1552, 34 U.S.P.Q. 2d 1210, pg 1559 (Fed. Cir. 1995). Applicants believe that the same holding applies to the present application.

The Federal Circuit describes the "obvious to try" standard as existing "when a general disclosure may pique the scientist's curiosity, such that further investigation might be done as a result of the disclosure, but the disclosure itself does not contain a sufficient teaching of how to obtain the desired result, or that the claims result would be obtained if certain directions were pursued." In re Eli Lilly & Co., 902 F.2d 945, 14 U.S.P.Q. 2d 1741 (Fed. Cir. 1990).

The references cited by the Examiner provide insufficient teaching regarding the methods needed to obtain modified gene fusion constructs having enhanced activity as claimed. The prior art cited in these references does not state the specifics of change addressed in the claims.

The PTO bears the burden of establishing a case of prima facie obviousness. In re Fine, 837 F.2d 1071, 1074 (Fed. Cir.1988). Therefore, in order to establish a prima facie case of obviousness, it is necessary for the examiner to present evidence, preferably in the form of some teaching,

suggestion, incentive or inference in the applied prior art, that one having ordinary skill in the art would have been led to combine the relevant teachings of the applied references in the proposed manner to arrive at the claimed invention. See e.g. Carella v. Starlight Archer, 804 F.2d 135 (Fed. Cir. 1986); Ashland Oil, Inc. v. Delta Resins & Refractories, Inc., 776 F.2d 281 (Fed. Cir. 1985).

It is submitted that it would not have been obvious for one of ordinary skill in the art to piece together the Applicant's specific method using the isolated disclosures cited by the Examiner. The Examiner has selected a combination of multiple references from which it is concluded the subject was obvious. For the factual and legal reasons presented herewith, the combination of references is insufficient to render the claimed invention obvious. It should be noted that it is clear that in order to establish a background for finding obviousness under 35 U.S.C. §103, that the determination of the scope and contents of the prior art cannot be performed by the mere gathering of elements from separate and distinct disclosures irrespective of the teachings of the disclosures. There must be a reason apparent at the time the invention was made to select the particular combination, or the references and the use of such teachings as evidence of obviousness will entail prohibited hindsight. In re Nomiya, 184 U.S.P.Q. 607 (CCPA 1975). One cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention. In re Fine, 5 U.S.P.Q. 2d. 1596 (Fed Cir. 1988)

Applicant respectfully submits that even in combination these references do not teach or suggest the claimed invention, so that the rejection is not supported. Applicant respectfully requests that the rejection of claims 6, 8, 15, 84, 85, 92 and 93 under 35 U.S.C. §103, be withdrawn.

Claim rejections under U.S.C. §112, first paragraph – Written Description

Claims 8, 41 and 105 are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention. Examiner states that Claims 8, 41 and 105, are directed to a method of producing a modified gene fusion construct which comprises two or more heterologous nucleic acid sequences encoding enzymatic domains selected from the group consisting of a genus of diaminobutyric acid aminotransferases, a genus of diaminobutyric acid acetyltransferases, and a genus of ectoine synthases which have not been adequately described in the specification. Examiner assert that the specification teaches the structures of only species of these enzymes which are isolated from the eubacteria H. elongate, and M. halophilus, and that the specification fails to describe any other representative species by any identifying characteristics or properties other than the functionality of being a diaminobutyric acid aminotransferase, a diaminobutyric acid acetyltransferase, or an ectoine synthase. Examiner concludes that given the lack of description of representative species encompassed by the genus of the claim, the specification fails to sufficiently describe the claimed invention in such full, clear, concise and exact terms that a skilled artisan would recognize that applicants were in possession of the claimed invention.

Applicant respectfully traverses and asserts that this is an improper standard.

As stated:

"Adequate description under the first paragraph of 35 U.S.C. §112 does not require literal support for the claimed invention....Rather, it is sufficient if the originally-filed disclosure would have conveyed to one having

ordinary skills in the art that an appellant had possession of the concept of what is claimed."

In Staehelin v. Secher, 24 USPQ 2d 1513 (B.P. A.I. 1992)

The Examiner is reminded that every species encompassed by the claimed invention need not be disclosed in the specification to satisfy the written description requirement of 35 USC §112, first paragraph. *Utter v. Hiraga*, 845 F. 2d 993, 6 USPQ2d 1709 (Fed. Cir. 1988). In fact, the description of a claimed genus can be by structure, formula, chemical name, or physical properties. See *Ex parte Maizel*, 27 USPQ2d 1662, 1669 (B.P.A.I. 1992), *citing Amgen v. Chugal*, 927 F. 2d. 1200, 1206 (Fed. Cir. 1991).

The description of a representative number of species does not require that the description be of such specificity that it would provide individual support for each species that the genus embraces. 66 Fed. Reg. 1099, 1106 (2000). Satisfactory disclosure of a "representative number" depends on whether one of skill in the art would recognize that the Applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed. 66 Fed. Reg. 1099, 1106 (2000). Applicants submit that the knowledge and level of skill in the art would allow a person of ordinary skill in the art to envision the claimed invention, namely the enzymatic domains from diaminobutyric acid aminotransferase, diaminobutyric acid acetyltransferase and ectonine synthase, all chemical structures well known in the art.

In addition, an Applicant may rely upon functional characteristics in the description, provided there is a correlation between the function and structure of the claimed invention. See the Guidelines of Examination of Patent Applications Under the 35 U.S.C. 112, first paragraph, "Written Description" Requirement, 66 Fed. Reg. 1099, 1106 (2000), citing the *Regents of the University of California v.*

Eli Lilly & Co., 119 F. 3d. 1559, 1569 (Fed. Cir. 1997) at 1568. Claims 8, 41 and 105 recite that the claimed method utilizes at least two enzymatic domains from diaminobutyric acid aminotransferase, diaminobutyric acid acetyltransferase and ectonine synthase, thereby providing a functional characterization of the compounds claimed in the genus.

In summary, the description of a representative number of species does not require the description to be of such specificity that it would provide individual support for each species that the genus embraces. Applicant submits that the relevant identifying physical, chemical and functional properties of the disclosed genus would be clearly recognized by one of skill in the art, and consequently, Applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus.

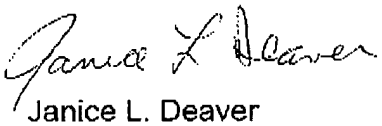
Applicant respectfully requests that the rejection of the claims under 35 U.S.C. §112, first paragraph for written description, be withdrawn.

Conclusion

In view of the above amendments and remarks, Applicant submits that the rejections of claims 1-6, 8, 11-20, 32-39, 41, 80, 82-95 and 105 under 35 U.S.C. §§102, 103 and 112 have been overcome. Applicant respectfully submits that this application is now in condition for allowance and requests that a timely Notice of Allowance be issued in this case.

If in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned.

Respectfully submitted,



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